REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. A response to the Final Office Action, Request for Continued Examination, and Request for Extension of Time was filed on December 21, 2007. Applicants subsequently received a Notice of Non-Compliant Amendment indicating an error in the amendments to the claims. Applicants inadvertently canceled claims 2-34 in the Request for Continuation Application Under 37 C.F.R. § 1.53(b) filed on September 15, 2003. Prior to the Notice of Non-Compliant Amendment, prosecution of the application on the merits had proceeded as if claims 2-34 were still pending.

In response to the Notice of Non-Compliant Amendment, claims 2-34 have been canceled without prejudice. New claims 36-68, which correspond to claims 2-34, have been added to the application to correct the inadvertent cancellation of claims. After entry of the amendment, claims 1 and 35-68 will be pending. New claims 36-48, 51-56, and 60-68 correspond to claims 2-14, 17-22, and 26-34, which were previously withdrawn by the Examiner as directed to non-elected subject matter.

Support for the amendment can be found in the specification, for example, at page 3, lines 8-9, page 10, lines 2-4, Fig. 15, and the claims as originally filed. Applicants submit the amendment does not raise any issues of new matter and places the claims in condition for allowance.

Enablement

Claims 15, 16, 23-25, and 35 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse this rejection.

Claims 15, 16, and 23-25 have been cancelled without prejudice. New claims 49, 40, and 57-59 correspond respectively to canceled claims 15, 16, and 23-25. Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claim 49 recites a method of inhibiting or attenuating differentiation of Th0 cells into a Th2 subtype, comprising administering to the Th0 cells an effective amount of a TCCR agonist antibody, or TCCR binding fragment thereof. Applicants reserve the right to pursue the canceled subject matter in a continuation application. Applicants submit claim 49 fully complies with the enablement requirement.

The Office continues to allege the specification does not enable administering any TCCR agonist, including TCCR agonist antibodies. Applicants respectfully do not agree.

There are many factors to be considered in an analysis of enablement, including breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples, and the quantity of experimentation. MPEP 2164.01(a) citing *In Re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Only a reasonable correlation between the specification and the scope of enablement is required.

The claims as amended recite administering a TCCR agonist antibody or antigen binding to Th0 cells. As discussed in the previous response, the working examples demonstrate inhibition of Th1 cytokine production and inhibition of Th1- mediated responses contrasted with exacerbated production of Th2 cytokines and exacerbated Th2 responses in TCCR-/- animals.

Further, the cytokines produced by Th1 cells and by Th2 cells each function to inhibit the other. As shown in the working examples, the lack of TCCR signaling results in the inability of differentiated T cells to produce Th1 cytokines, whereas production of Th2 cytokines is enhanced.

In the absence of TCCR receptor activation, an exacerbated Th2 response was induced. The exacerbated Th2 response was evidenced both by Th2-mediated immune response and by production of Th2 cytokines from T cells obtained from the TCCR-/- mice. These TCCR deficient mice and cells obtained from such mice exhibited a reduced Th1 response. Reduced Th1 cytokine production by T cells obtained from TCCR-/- mice, decreased total serum IgG2a, reduced titers or IgG2a in response to *in vivo* challenge with ovalbumin, and the inability to mount a Th1 response to bacterial infection fully demonstrate reduced development of Th1 cells in TCCR-/- mice. These data provide guidance about the role of TCCR receptor activation in mediating Th0 cell differentiation, and reasonably suggest that replacement of TCCR signaling with a TCCR agonist will inhibit or attenuate the exacerbated Th2 response and restore the diminished Th1 response. This guidance is consistent with the claimed methods.

Contrary to the Examiner's assertions, Lucas *et al.* and USSN 11/275,181 (hereinafter the '181 application) confirm Applicants' teachings. Lucas *et al.* discloses further studies into the mechanism of TCCR-mediated immune response, using the discovered TCCR ligand, IL27. The publication confirms a role for TCCR signaling in the suppression of Th2-mediated disease.

Lucas *et al.* describes the effect of IL27/TCCR activation on "the master switch" for Th2 development, GATA3.

> Although IL-27 does not drive the differentiation process of $CD4^+$ cells toward an IFN-γ-secreting phenotype on its own, it certainly represents an important early trigger for TH1 differentiation *in vivo*, as demonstrated by the increased initial susceptibility of *TCCR*$^{/wsx-1}$ knockout mice to infection with intracellular pathogens (16, 17). Our *in vitro* studies show that IL-27, an early product of activated antigen-presenting cells (18), acts on naïve $CD4^+$ T cells by inducing IL-12 responsiveness by means of induction of T-bet and suppression of GATA-3. Therefore, at the time of activation of naïve $CD4^+$ T cell[s] by antigen-presenting cells *in vivo*, IL-27 functions in a paracrine manner to establish IL-12 responsiveness of early developing T_H cells, and consequently contributes to bias the T cell response toward a T_H1 outcome. (Lucas *et al.* at page 15052).

Lucas *et al.* also demonstrate that IL-27 provides an IFN-γ-independent signal for the induction of T-bet in developing T_H cells, and confirm that the TCCR agonist, IL-27, not only induces T-bet, leading to a T_H1 outcome, but "provides an alternative signal for GATA-3 suppression" thereby suppressing development of T_H2 cells and a T_H2 cell response (Lucas *et al.* at page 15052). Accordingly, Applicants assert the claimed methods are confirmed and supported by Lucas *et al.*

The Office Action alleges the '181 application does not provide a sufficient nexus between the functional activities of antibody 2686, a TCCR agonist antibody, and inhibiting or attenuating the differentiation of Th0 cells into the Th2 subtype because the Ba/F3 cells in Example 6 of the '181 application are not T cells. Applicants respectfully do not agree. The '181 application was cited for the purpose of confirming that TCCR agonist antibodies are capable of binding to TCCR expressed by a cell and inducing a TCCR-mediated biological activity. Proliferation of the Ba/F3 cells was mediated by binding of the TCCR agonist antibody to the recombinantly expressed human TCCR. Example 6 of the '181 application confirms that a TCCR agonist antibody, such as the antibody 2686, can bind and stimulate human TCCR expressed by a cell to induce a TCCR-mediated biological activity, such as cell differentiation or cell proliferation.

As discussed above, the claims as amended are directed to inhibiting or attenuating differentiation of Th0 cells into a Th2 subtype with an effective amount of a TCCR antibody, or TCCR binding fragment thereof. The specification teaches that TCCR signaling induces differentiation of Th0 cells into Th1 cells, and inhibits or attenuates differentiation of Th0 cells

into Th2 cells. The specification further TCCR asserts signaling with a TCCR agonist such as an agonist antibody will inhibit or attenuate the exacerbated Th2 response and restore the diminished Th1 response.

These teachings are confirmed by subsequent publications. Pflanz *et al.*, 2002, *Immunity*, 16:779-790 (copy enclosed) confirms that a TCCR agonist, IL-27, induces naïve CD4+ T cells (Th0 cells) to differentiate into Th1 cells but not Th2 cells (Pflanz *et al.* at Figs. 5 and 6). Lucas *et al.*, as discussed above, confirms the TCCR agonist IL-27 provides an IFN-γ-independent signal for the inducing factor T-bet, leading to a T_H1 outcome, as well as inducing an alternative signal for GATA-3 suppression, thereby suppressing development of T_H2 cells and suppressing T_H2 cell response (Lucas *et al.* at page 15052). The '181 application, as discussed above, confirms that a TCCR agonist antibody, such as antibody 2686, is capable of binding to TCCR expressed by a cell and the agonist binding stimulates/induces a TCCR-mediated biological activity (See, Example 6, '181 application) in the cell.

In view of the guidance and working examples provided in the specification and the confirmatory evidence provided by Pflanz *et al.*, Lucas *et al.*, and the '181 application, Applicants respectfully submit the specification provides sufficient evidence that administering a TCCR agonist such as a TCCR agonist antibody, would be reasonably expected to inhibit or attenuate differentiation of Th0 cells into the Th2 subtype. Based on the teachings of the specification, the full scope of the claims as amended can be practiced without undue experimentation. Withdrawal of the enablement rejection is respectfully requested.

Written Description

Claims 15, 16, 23-25, and 35 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants respectfully traverse this rejection.

Claims 15, 16, and 23-25 have been cancelled without prejudice. New claims 49, 40, and 57-59 correspond respectively to canceled claims 15, 16, and 23-25.

The Office Action alleges the specification fails to contain sufficient written description of any TCCR agonists. Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claim 15 has been amended to recite a method of inhibiting or attenuating differentiation of Th0 cells into a Th2 subtype, comprising administering to the Th0

cells an effective amount of a TCCR agonist antibody, or TCCR binding fragment thereof. Applicants reserve the right to pursue the canceled subject matter in a continuation application.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. MPEP § 2163(I) (emphasis added). As discussed above for enablement, the specification provides adequate description of the structure of TCCR and its role in the development of T cells and T cell responses.

Applicants also direct the Examiner's attention to Example 16 in the Revised Written Description Guidelines Training Materials. Example 16 outlines a written description analysis of an antibody claim that satisfies the requirement under 35 U.S.C. § 112, first paragraph. The claim in Example 16 is directed to a genus of antibodies capable of binding antigen X. The specification provided a clear protocol by which antigen X was isolated. Antigen X was purified by gel filtration and found to have a molecular weight of 55 KD. The specification did not disclose antibodies that specifically bind antigen X in an example. Example 16 in the written description guidelines states:

> Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.

Similar to the claim analyzed in Example 16 of the written description guidelines, Applicants' claims encompass a genus of antibodies that bind TCCR. Examples 1 and 4-7, in the specification describe TCCR nucleic acid and amino acid sequence, and how to isolate cDNA clones encoding TCCR and express TCCR in cells. Example 8 describes production of antibodies that specifically bind TCCR. The specification describes methods for identifying TCCR agonists, including TCCR agonist antibodies. See, for example, the specification at pages 63-65.

Applying the analysis set forth in Example 16 of the written description guidelines, Applicants submit the specification sufficiently describes the genus of antibodies. Considering the high and advanced level of skill in the art of antibody production, one skilled in the art would

have recognized that the spectrum of antibodies that bind TCCR were implicitly disclosed as a result of the isolation of TCCR. The spectrum of antibodies that bind TCCR would include those agonist Ab that stimulate TCCR signaling and are useful in the claimed method invention.

For at least these reasons, Applicants respectfully submit the specification fully describes the claimed invention. Removal of the written description rejection is respectfully requested.

Provisional Double Patenting

Claims 15, 16, 23-25, and 35 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of U.S. Patent Application No. 10/088,950. Applicants acknowledge the rejection and respectfully request that the rejection be held in abeyance until notice of allowable subject matter.

New Matter

Claims 15, 16, 23-25, and 35 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection. Applicants respectfully traverse the rejection.

Claims 15, 16, and 23-25 have been cancelled without prejudice. New claims 49, 40, and 57-59 correspond respectively to canceled claims 15, 16, and 23-25.

The claims have been amended to clarify that the undifferentiated T cells are Th0 cells. Support for the amendment can be found in the specification, for example, at page 3, lines 8-9, page 10, lines 2-4, and Fig. 15. The phrase "induce a TCCR-mediated response" has been removed from the claims.

Withdrawal of the new matter rejection is respectfully requested.

Conclusion

In view of the above amendments and remarks, Applicants respectfully submit the claims are in condition for allowance and request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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